REMARKS

I. Amendments to the Claims

Claims 1-15 are pending in this application. Claims 16-24 are withdrawn. Claim 1 has been amended to recite "rapidly dispersing microgranules consisting essentially of ..." Support for this amendment can be found throughout the specification, for example at paragraphs [0018]-[0019], and [0027]. No new matter has been added by reason of this amendment.

II. Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-15 under 35 U.S.C. §103(a) as allegedly obvious over *Gowan* (US 5,876,759) in view of *Ohta* (EP 0914818) and *Guo* (US 2004/0068000). Applicants respectfully disagree because the combination of the cited references (a) fail to support a *prima facie* case of obviousness and (b) require the use of impermissible hindsight in order to combine them in the particular manner proposed by the Examiner.

Claimed Invention

The claimed tablet rapidly disintegrates in the oral cavity and comprises at least two types of granules compressed together: (a) rapidly dispersing microgranules (RDMs) consisting essentially of a sugar alcohol or a saccharide, or a mixture thereof, having an average particle size not more than about 30 microns, ***and*** a disintegrant, and (b) "taste-masked microcapsules" prepared by encapsulating a wet milled, "granulated mass" containing "at least one drug" and "at least one polymeric binder".

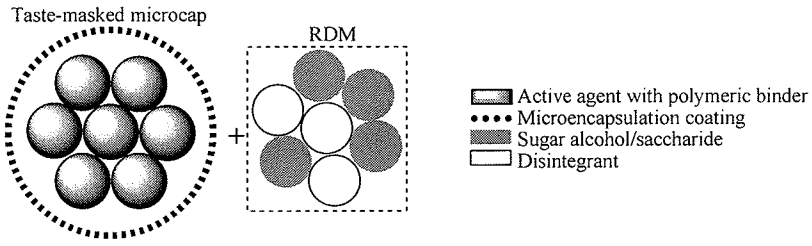
Thus, the taste-masked microcapsules of the claimed invention are agglomerates comprising "at least one drug" and "at least one polymeric binder", and by virtue of the wet milling process, possess different physical properties compared to drug particles prepared by other methods – e.g., are "hard, flexible, [and] less friable" and do not have the undesirable levels of "fines" which result from dry milling.[1] In addition, the RDMs of the claimed invention are agglomerates consisting essentially of "not more than about 30 micron" sugar

[1] Present specification, ¶ [0015].

alcohol and/or saccharide and a disintegrant. (*See* Figure 1, below, which shows an embodiment of the claimed invention.)

Embodiment of Claimed Invention: Taste-Masked Microcapsules and RDM

FIGURE 1



Gowan

Gowan describes a compressed, orally disintegrating dosage form prepared by dry-blending: (a) drug particles having a taste-masking coating; (b) a water-disintegratable, compressible carbohydrate; and (c) a binder. (*See* Figure 2, below). *Gowan* explains that "[t]he ingredients are dry blended and then compressed into a mass, preferably a wafer." (Col. 3, lines 2-5). Thus, *Gowan*, discloses a tablet comprising at least ***three*** separate types of particles: taste-masked drug particles, a compressible carbohydrate, and a binder. Applicants note that the required binder component of *Gowan* is *external* to the taste-masked drug particles, instead of *within* the taste-masked drug particle as in the claimed invention. Further, *Gowan* fails to disclose any information regarding friability or levels of fines for the drug particles.

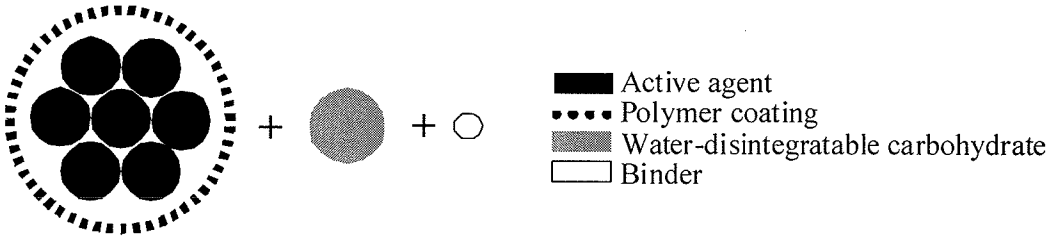
In one embodiment, *Gowan* notes (Col. 5, lines 40-52):

> [t]he blend of first and second polymers may be coated directly onto the pure pharmaceutical or may be coated onto a granulated particle containing the pharmaceutical. In the case of a granulated particle, such as a rotogranulated particle, the pharmaceutical active will constitute from about 5 to about 90 weight percent of the particle, with the remainder being the binder or filler. Suitable binders for the granulated particles

include polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, and other pharmaceutically acceptable polymers. Fillers suitable for use in such granulated particles include lactose, confectioner's sugar, mannitol, dextrose, fructose, other pharmaceutically acceptable saccharides and microcrystalline cellulose.

The formulation described above in *Gowan* can be illustrated as shown in Figure 2 (wherein the "active agent" component in Fig. 2 represents the granulated particle which can include an active agent in combination with binder(s) or filler(s)).

FIGURE 2



As can be seen in Figure 2, *Gowan's* formulation does not include the RDMs of the claimed invention (which are agglomerates of the constituent sugar alcohol and/or saccharide particles and disintegrant particles). In fact, *Gowan* fails to even disclose the disintegrant component of the claimed RDMs. The Examiner apparently asserts that *Gowan* does teach disintegrants, by equating the polyvinylpyrrolidone binder of *Gowan* with crospovidone, a disintegrant.[2] However, polyvinylpyrrolidone and crospovidone are chemically distinct in structure and properties. Polyvinylpyrrolidone is an uncrosslinked homopolymer of vinylpyrrolidone, is water soluble, and is a well-known binder, thickening agent, adhesive, and film-forming agent.[3] Crospovidone, in contrast, is crosslinked and insoluble, and is a well-known disintegrant by virtue of its ability to swell in contact with water.[4] Thus, one of skill in the art would not consider the polyvinylpyrrolidone binder of *Gowan* to be a

[2] Advisory Action, dated 10/5/2010, continuation sheet at paragraph 2.
[3] *See* e.g., BASF Technical Specifications for Soluble Kollidon® grades.

disintegrant.

Furthermore, even if *Gowan* did teach a disintegrant (which it does not, as discussed above), *Gowan's* disclosed particle would not be equivalent to the RDMs of the claimed invention. As noted in above and in Figure 1, the claimed invention has at least two separate particles – an RDM and a taste-masked microcapsule. If the particles of *Gowan* were interpreted to correspond to the taste-masked microcapsules of the claimed invention, the compositions of *Gowan* would lack the RDMs of the claimed invention.

Furthermore, even if the particles of *Gowan* were interpreted as corresponding to the RDMs of the claimed invention, they would comprise an active agent combined with a "disintegrant" (actually, a binder) and a sugar or sugar alcohol. However, as amended, the claimed invention recites RDMs "consisting essentially of a sugar alcohol or a saccharide or a mixture thereof having an average particle size not more than about 30 microns, and a disintegrant." Applicants respectfully submit that the particles of *Gowan*, even if interpreted as including a disintegrant, would be excluded as RDMs, as the active agent component of the particles of *Gowan* – which is not present in the claimed RDMs – would reasonably be expected to "materially affect the basic and novel characteristic(s)" of the claimed invention.[5]

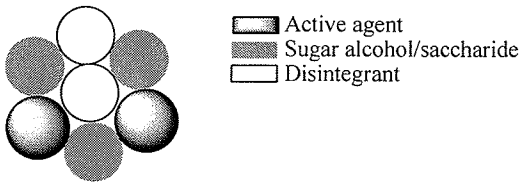
Thus, *Gowan* necessarily fails to teach the RDMs of the claimed invention, because *Gowan* fails to teach disintegrants, let alone the combination of a sugar alcohol or a saccharide and a disintegrant. Furthermore, *Gowan* fails to teach the combination of taste-masked microparticles and RDMs.

Ohta

Ohta describes tablets comprising a single type of drug-containing granule, prepared by granulating together a sugar alcohol or saccharide, a disintegrant, ***and a drug***, which are then compressed into a rapidly disintegrating tablet (Figure 3, below).

[4] *See*, e.g, BASF Technical Specifications for Insoluble Kollidon® grades.
[5] MPEP 2111.03.

FIGURE 3



As shown in Figure 3, above, the compositions of *Ohta* have only one type of granule, and these granules do not have any kind of coating – taste-masking or otherwise.

As amended, the claimed invention recite RDMs "consisting essentially of a sugar alcohol or a saccharide or a mixture thereof having an average particle size not more than about 30 microns, and a disintegrant." Applicants respectfully submit that the granules of *Ohta* would be excluded as RDMs, as the active agent component of the granules of *Ohta* – which is not present in the claimed RDMs – would reasonably be expected to "materially affect the basic and novel characteristic(s)" of the claimed invention.[6]

In addition, as noted above, the drug-containing granules of *Ohta* are uncoated, and thus would not be expected to have taste-masking properties, whereas the drug-containing microcapsules of the claimed invention are expressly "taste-masked" by microencapsulation. Applicants respectfully submit that the drug-containing microgranules of the claimed invention would thus be distinct from the uncoated granules of *Ohta*.

Furthermore, Applicants note that the claimed invention includes at least two types of particles: the taste-masked microcapsules, and RDMs. Even if the granules of *Ohta* were considered to be taste-masked microcapsules according to the claimed invention (which they are not, as discussed above), *Ohta's* composition would lack the RDMs of the claimed invention. Conversely, even if the granules of *Ohta* were considered to be RDMs (which they are not, as discussed above), *Ohta's* composition would lack the taste-masked microcapsules of the claimed invention.

Thus, *Ohta* fails to disclose the taste-masked microcapsules, RDMs, and the combination thereof, of the claimed invention.

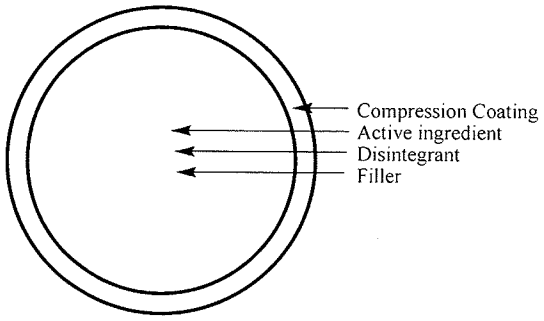
[6] MPEP 2111.03.

Guo

Guo describes a "compression coated solid dosage form"[7] (*i.e.*, tablet) for oral administration that comprises a core prepared by compressing a mixture of a "bitter or unpleasant tasting" active, along with excipients such as fillers (*e.g.*, lactose, microcrystalline cellulose, etc.), and disintegrants (*e.g.*, croscarmellose sodium)[8], then coated with a compression coating having a thickness "of 0.1 mm to 5 mm." (*See* Figure 4, below). Applicants note that the compression coating of *Guo* covers the *entire* dosage form (i.e., tablet), not the individual drug-containing granules comprising the tablet as required by the claimed invention, and *Guo* fails to disclose separate particles which are agglomerates of a sugar alcohol and/or saccharide and a disintegrant (i.e., the RDMs of the claimed invention).

In addition the "compression coated solid dosage form" of *Guo* is clearly designed to be swallowed whole, and not disintegrate in the oral cavity, as for the claimed invention, because disintegration of the compression coating in the mouth would cause the "bitter or unpleasant tasting" active to be released, and thus defeat the taste-masking feature of the compression coating.

Figure 4



Thus, *Guo* describes a taste-masking coating over an entire tablet, and therefore fails to disclose: (a) individually taste-masked particles comprising the combination of a drug and a binder; (b) RDMs consisting essentially of the combination of ≤ 30 μm sugar alcohol or saccharide particles and a disintegrant; and (c) the combination of individually taste-masked

[7] US 2004/0068000, ¶ [0006] (hereinafter "*Guo*").

microcapsules and RDMs). Furthermore, *Guo* fails to disclose the orally disintegrating tablet of the claimed invention.

No *Prima Facie* Obviousness

As discussed above, the claimed tablet that rapidly disintegrates in the oral cavity comprises at least two particles: RDMs consisting essentially of a sugar alcohol and/or saccharide in combination with a disintegrant, and taste-masked microcapsules comprising at least one drug and at least on polymeric binder (prepared by wet milling and microencapsulation).

However, *Gowan* does not even disclose disintegrants, let alone RDMs, and thus necessarily cannot teach or suggest the RDMs of the present invention, which require a disintegrant component.

Ohta only describes compositions comprising a single, drug-containing particle, whereas the claimed RDMs cannot include a drug.

Guo describes a tablet core prepared by compressing a blend of drug and excipients, and does not disclose a single type of particle which is an aggregate consisting essentially of a sugar alcohol/saccharide and disintegrant, as in the RDMs of the claimed invention. Furthermore, since *Guo's* tablet is not intended to rapidly disintegrate in the oral cavity, *Guo* reasonably could not suggest the RDMs of the present invention, which provide for rapid disintegration in the mouth.

Therefore, as each of the references individually fail to teach the RDMs of the claimed invention, the combination of the cited references necessarily fails to teach or suggest RDMs, and thus fails to support *prima facie* obviousness.

Applicants therefore request that the rejection be withdrawn.

Claim 3

Applicants also respectfully submit that the Examiner has not established a *prima facie* case of obviousness with regard to claim 3. Claim 3 recites "said microgranule exhibiting not more than 15% fines (passing through 140 mesh screen) when tested in

[8] *Guo* at p. 3, Example 1.

accordance with the procedure for friability test." As the specification notes at [0066], "granules must have the property of maintaining their integrity during handling and processing . . . [and] should exhibit sufficient strength and sufficiently low friability to withstand attrition during the handling or processing, such as microencapsulation."

In response to previous arguments by the Applicants "that none of the references disclose the said microgranule exhibiting not more than 15% fines," the Examiner asserts that "*Gowan* teaches that coated acetaminophen particles passed through a 30 mesh screen and components are compressed into tablets having a hardness less than 1.0 Kp result in a dosage form exhibiting high friability."[9] Applicants respectfully disagree with the Examiner's assertion that *Gowan* as cited, in addition to any of the other references, teaches the invention in claim 3.

Fines, as used in the claimed invention, describes under-sized particles as compared to the desired particle size distribution.[10] As noted in the specification, "it is a challenge to taste mask such fine powders . . . [O]rdinary wet granulation methods using a widely used binder, such as Povidone (polyvinylpyrrolidone), produce fragile/friable granules which break down or fracture due to rapid agitation during microencapsulation by coacervation."[11] The claimed invention provides for compositions and methods that cure the problem of unacceptable levels of fines in commercial products. None of the references cited expressly disclose this property of reduced fines of claim 3, or provides for granulation and wet milling of a mixture comprising a drug and a binder to provide drug-containing microgranules having such properties.

Furthermore, the claimed friability/fines property is not inherent in the cited references, since properties such as friability and percentage of fines are reasonably dependent on composition and processing conditions. Accordingly, such properties are reasonably not necessarily (i.e., inherently or inevitably) present in the compositions of the cited references, since, as discussed above, the compositions of *Gowan*, *Ohta*, and *Guo* are quite different from the claimed compositions. Thus, Applicants submit that the Examiner

[9] October 5, 2010 Advisory Action, p. 3.
[10] Present specification, ¶ [0012].
[11] *Id.*

has failed to show, as is necessary under MPEP 2112, that the ODT disclosed in *Gowan* inherently contains the necessary percentage of fines to fall under claim 3.

As each of the references individually fail to teach this limitation of claim 3, the combination of cited references necessarily cannot cure this deficiency, and thus fails to support *prima facie* obviousness in regard to claim 3.

Applicants therefore request that the rejection be withdrawn.

Hindsight Combination of References

The Examiner suggests that one skilled in the art would have been motivated to combine the compressed dosage forms of *Gowan* with the sugar alcohol or saccharide granules of *Ohta* to provide a rapidly disintegrating tablet according to the presently claimed invention. The Examiner argues that the motivation for the combination would have come from the desire to reduce the undesirable taste or bitterness of the *Gowan* tablet and to provide a pleasant taste perception.

However, as discussed above, Applicants note that the particles of *Ohta* are not taste-masked. Applicants submit that one would not reasonably combine the taste-masked particles of *Gowan* with the non-taste-masked particles of *Ohta*, because to do so would defeat the intent of *Gowan* to provide taste-masked compositions which can be used for "pharmaceuticals having an objectionable taste."[12]

Moreover, even if, for example, *Gowan*, *Ohta*, and *Guo* were combined, there are many different equally reasonable combinations which would not provide the claimed tablet. For instance, one reasonable combination would be, as the Examiner suggests, to simply add the sugar alcohol or saccharide of *Ohta* to the three-part compression dry-blend of *Gowan*. The resulting tablet would simply be a compressed four-component dry-blend, and would still not include the RDMs of the claimed invention, which are agglomerates of at least a sugar alcohol/saccharide and a disintegrant. Alternatively, the taste-masked drug-containing particle of *Gowan* could replace the drug particles of *Guo*, or the compression coating of *Gowan* could be used to provide taste-masking for the tablets of *Ohta*. The former combination would still lack the RDMs of the claimed invention, and the latter would lack

individually taste-masked drug-containing microcapsules of the claimed invention. Thus, none of these equally reasonable combinations of the cited references would provide the claimed invention.

Moreover, elements within each of the references suggest combining the cited references in a manner leading away from the claimed invention. For example, rather than suggesting the necessity of a RDM particle comprised of a disintegrant and a sugar or sugar alcohol, *Gowan* implies that a disintegrant is wholly unnecessary in an orally disintegrating tablet (ODT) formulation, since *Gowan* does not even mention disintegrants, and teaches that oral disintegration can be provided using only a "compressible carbohydrate" component (which also lacks the ≤ 30 μm particle size of the sugar alcohol or saccharide component of the claimed rapid releasing microgranules). Further, *Ohta* teaches tablets comprising a single type of particle including all of the constituent components of the tablet, in which the drug-containing particles are not taste-masked. Finally, *Guo* suggests that taste-masking can be achieved by encapsulating the entire tablet in a compression coating rather than providing individually taste-masked drug-particles microcapsules as described in the claimed invention. (In addition, use of *Guo's* compression coating would reasonably prevent such tablets from rapidly disintegrating in the oral cavity as in the claimed invention). Thus, the cited references as reasonably direct one to tablets lacking RDMs (*Gowan*), tablets lacking taste-masking entirely (*Ohta*), or non-orally disintegrating tablets lacking individually taste-masked drug-containing microparticles (*Guo*).

Since the references themselves do not direct one to the particular combination suggested by the Examiner, and indeed as reasonably could be combined in a manner which would not provide the claimed invention, Applicants submit the Examiner has improperly used hindsight knowledge of Applicants' invention in proposing the asserted combination of the cited references. Accordingly, Applicants request that the rejection be withdrawn.

Rejoinder of Claims 16-24

Applicants respectfully submit that the withdrawn claims recite all of the limitations of the pending claims under examination. For example, independent claim 16 recites a

[12] *Gowan*, col. 3, lines 13-14

method for preparing a tablet that disintegrates in the oral cavity, prepared by granulating, wet milling, and microencapsulating a pharmaceutically acceptable formulation comprising at least one drug; preparing rapidly dispersing microgranules comprising a sugar alcohol or saccharide having an average particle size of not less than 30 μm, and a disintegrant; and compressing the drug-containing particles and rapidly releasing granules to form a tablet from which not less than 60% of the drug dissolves in about 60 minutes. The remaining withdrawn claims all depend from claim 16, directly or indirectly, and thus include these limitations. Since, for the reasons discussed above claims 1-15 are allowable, the withdrawn claims should be rejoined.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-1283. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. 1.136(a)(3).

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